Editorial

Heart failure: vive la difference!

The clinical diagnosis of heart failure is independent of aetiology. Treatment strategies are aimed at alleviation of symptoms with diuretics and digoxin, and the improvement of cardiac function and prognosis with vasodilators and angiotensin converting enzyme (ACE) inhibitors. The impact of aetiology on management has largely been ignored. Recent clinical trials have indicated that patients with idiopathic dilated cardiomyopathy may respond differently from those with left ventricular dysfunction due to ischaemic heart disease.

ACE inhibitors

Early studies of ACE inhibitors recruited patients according to the severity of symptoms or degree of left ventricular dysfunction without specifying cause. However, two studies suggested that the benefit of ACE inhibition was greater in patients with heart failure caused by non-ischaemic cardiomyopathy. The Second Veteran's Cooperative Administration trial found a reduction in annual mortality rate to 14.1% in those with coronary artery disease and 10.7% in those without underlying ischaemia when treated with enalapril.[1] In one of the SOLVD studies, treatment with enalapril resulted in a 12% risk reduction for death compared to placebo in patients with an ischaemic cause for left ventricular dysfunction, compared with a 27% risk reduction for those with another cause of heart failure.[2] It is interesting that patients with non-ischaemic cardiomyopathy have greater benefit from treatment with ACE inhibitors, as it has been suggested that this group of drugs has anti-ischaemic properties.[3]

β Blockers

The beneficial effects of β adrenergic blockade following myocardial infarction are well documented, regardless of evidence of cardiac failure.[4] A direct comparison of efficacy in non-ischaemic heart failure has not been performed, although beneficial effects on morbidity have been documented in idiopathic dilated cardiomyopathy with metoprolol.[5] In a recent trial using bisoprolol, patients were randomised on the basis of left ventricular ejection fraction with 40% as the cut off point.[6] Although no overall mortality benefit was found, retrospective subgroup analysis revealed a significant reduction in mortality in those with non-ischaemic cardiomyopathy receiving bisoprolol, from 22.5% to 12%, but no improvement in those with a history of myocardial infarction. However, the recent trial using carvedilol in heart failure produced a reduction in mortality with no difference between ischaemic and non-ischaemic cardiomyopathy patients.[7]

Arrhythmias

Arrhythmic death is common in patients with heart failure. However, differences in outcome dependent on the origin of heart failure may be apparent in treatment with amiodarone. The GESICA trial was an Argentinean multicentre, randomised investigation of the use of amiodarone in severe heart failure,[8] with an additional stratification according to the presence or absence of non-sustained ventricular tachycardia. A risk reduction of 28% was found in those receiving treatment, a result that contrasted with the absence of effect in the later North American CHF-STAT trial of amiodarone in patients with congestive heart failure and 10 or more extrasystoles.[9] The trial populations were different in that 60% of patients had non-ischaemic heart failure in the Argentinean study compared with only 29% in the American trial. Subgroup analysis of outcome according to aetiology in CHF-STAT revealed a trend towards increased survival in patients with non-ischaemic cardiomyopathy receiving amiodarone. These data suggest that the overall positive results of the GESICA trial could be due to the greater impact of amiodarone in non-ischaemic heart failure.

Calcium channel blockers

A difference in effect of treatment in ischaemic and non-ischaemic cardiac failure has recently been noted in the trial, prospective randomised amlodipine survival evaluation.[10] Amlodipine reduced risk of death from all causes by 16% in patients with an ejection fraction below 30%. Among patients with ischaemic heart disease, there was no difference in the primary end point but in those with non-ischaemic heart failure, risk of death was reduced by 46%. Such an effect has not been noted in other trials of calcium channel antagonists.

What could be the explanation for these differences?

Idiopathic dilated cardiomyopathy causes global dysfunction of the ventricle as the disease process affects the heart uniformly. This causes stretch of all myocytes, resulting in increased contractility according to Starling's law. Ultimately, myocardial contractility declines when myocytes are overstretched. Reduction of this stretch allows the myocyte to recover contractile function. Strategies to reduce excessive stretch should improve contractility—indeed, ACE inhibitors and β adrenergic antagonists reduce left ventricular dimensions and improve ejection fraction.[5 10] In patients with dilated cardiomyopathy due to a non-progressive insult such as viral myocarditis, deterioration occurs in the long term because of overstretch and not because of recurrent injury. Reduction of this cardiomyopathy of overload could result in long term improvement.[11]

This contrasts with patients who have left ventricular dysfunction due to ischaemia, in whom disease will inevitably be segmental. Segmental disease is more likely to produce eccentric ventricular dilatation. Scar tissue resulting from myocardial infarction is incapable of recoil and remains passive. Only the functioning surrounding myocardium, which is stretched as a consequence of the scar tissue, can be improved. It is therefore conceivable that the size of benefit from reduction of wall stress will be less in this group of patients compared with the improvement in global function that may be achieved in those with non-ischaemic dilated cardiomyopathy. In both cases, myocytes will eventually die and be replaced by fibrous tissue. At this stage, no treatment is likely to be of significant benefit.

As more treatments become available for the management of heart failure, their choice and success may increasingly depend on the aetiology of heart failure. Future trials should

examine outcome in terms of cause. Heart failure remains a clinical syndrome and the selection of the optimum strategy is already becoming individualised.

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